Myocardial Infarction Guided Emergency Hematopoiesis

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“Emergency hematopoiesis” occurs after myocardial infarction (MI) and includes different processes: (1) the amplification of leukocyte production, (2) the maturation of alternative leukocyte subsets and (3) the release of myeloid cells from primary and secondary hematopoietic organs.

myocardial infarction hematopoiesis myeloid cells extracellular signaling

1. Myocardial Infarction Guided Emergency Hematopoiesis

While hematopoiesis continuously supplies new blood cells in homeostatic conditions, hematopoiesis may react to external stressors/triggers. The response of the hematopoietic system is driven by several signals, either local or external. In case of myocardial infarction (MI), cardiac cells (such as mast cells, macrophages, and cardiomyocytes (CM)) trigger a massive recruitment of circulating leukocytes through the release of soluble factors. In parallel, the bone marrow (BM) responds to the remote injury by releasing hematopoietic progenitors, expanding the immune cell pool and promoting the maturation of distinct leukocyte subsets [1]. To meet the high demand of leukocytes, hematopoiesis may also take place outside the BM, in the spleen (extramedullary hematopoiesis) [2][3][4][5][6]. “Emergency hematopoiesis” occurs after MI and includes different processes: (1) the amplification of leukocyte production, (2) the maturation of alternative leukocyte subsets and (3) the release of myeloid cells from primary and secondary hematopoietic organs.

2. Progenitor Amplification

The BM responds to MI and transiently increases production of leukocytes. This process passes through the amplification of hematopoietic progenitor cells in the BM. Indeed, positron emission tomography (PET) analysis of the pelvic bone in patients with MI showed increased metabolic activities in the BM, probably reflecting increased proliferation of hematopoietic stem cells (HSCs). In line, the analysis of murine models showed that MI drives the activation of Wnt pathway, which regulates the proliferation of hematopoietic stem and progenitor cells (HSPCs) [7]. In a study by Dutta and colleagues, it was shown that MI supports the proliferation of $CCR2^{+}$ HSCs. Through the expression of Mtg16, $CCR2^{+}$ (CC motif chemokine receptor 2 (CCR2)) progenitors are biased toward a myeloid phenotype, thus present a source of neutrophils, monocytes and macrophages, the cellular protagonists of the inflammatory phase following MI [8]. Using parabiosis, mice with a joined circulation, and left anterior descending (LAD) coronary artery ligation, the same research group demonstrated that MI increased levels of blood-borne,

circulating factors that stimulate proliferation of HSCs. In particular IL-1β, binding the receptor (IL-1R1) expressed by HSCs and non-hematopoietic cells of the niches, induced activation of the BM and production of neutrophils and monocytes [9].

Together with IL1β, several other factors act directly on hematopoiesis during the inflammatory phase of the MI including granulocyte colony-stimulating factor (G-CSF), granulocyte–macrophage colony-stimulating factor (GM-CSF), CXCL12 and CCL2. These factors can modulate proliferation and differentiation of hematopoietic progenitors during the course of MI [10][11].

G-CSF induces maturation, survival, proliferation, and functional activation of granulocytes. Moreover, it also plays a crucial role in the mobilization of granulocytes and HSPCs from the BM into the peripheral circulation [10][12]. Indeed, G-CSF inhibits macrophage-mediated retention signals in the BM and enhances sympathetic nervous system (SNS)-mediated progenitor release [13]. As mentioned before, the SNS has a fundamental role in homeostatic hematopoiesis. Additionally, the SNS is also involved in the regulation of the BM in case of MI. Noradrenaline increased in the BM of mice after MI. As consequence, Nes^{+} mesenchymal stem and stromal cells (MSC), expressing β3AR, decrease the expression of Cxcl12 and Scf. The downregulation of those retention factors stimulates the release of HSCs into the blood [14]. Due to the capability to regulate different processes, the role of G-CSF in case of MI has been extensively studied, especially as possible pro-regenerative treatment. However, results from studies that evaluated the therapeutic potential of G-CSF are conflicting. Several studies showed that G-CSF treatment, administered before and after MI onset, may be beneficial inducing a better regeneration of cardiac tissue. On the other hand, more recent studies showed that G-CSF fuels inflammation in the cardiac tissue [15][16][17].

GM-CSF is produced by different cell types including leukocytes, fibroblasts and endothelial cells (ECs). Like in the case of G-CSF, GM-CSF induces BM cell mobilization and was thus studied as pro-regenerative factor after MI. Alone or in combination with other cytokines, G-CSF can stimulate survival, proliferation and differentiation of different myeloid cells like neutrophils, eosinophils, monocytes and dendritic cells (DCs). In particular GM-CSF, in combination with tumor necrosis factor-α (TNFα) and IL4, induces the differentiation of myeloid cells into DCs [12]. Although GM-CSF may confer cardiac reparative benefits when administered together with other growth factors, current evidence suggests that GM-CSF-induced cellular infiltration and molecular changes cause more damage than benefits in the post-infarction period. A study conducted by Anzai and colleagues showed that cardiac fibroblasts are the major source of GM-CSF in the first days after MI, in both mice and humans. GM-CSF is produced in the infarcted heart and promotes myelopoiesis in the BM by targeting a specific progenitor subset that gives rise to neutrophils and $Ly6C^{HI}$ monocytes. Moreover, the same study showed the GM-CSF impairs wound healing through increased leukocyte accumulation after MI (primarily neutrophils and monocytes). Indeed, GM-CSF induces expression of immune cell-attracting chemokines such as Cxcl2, Ccl2, Ccl3, Ccl5, and Ccl7 [18].

HSCs express MCSF1R, the receptor for macrophage colony-stimulating factor (M-CSF), and react to M-CSF stimulation with differentiation toward monocytes in vitro. Indeed, M-CSF is a cytokine that regulates the differentiation, proliferation, and survival of monocytic progenitor cells [19][20]. In steady state mice, perivascular

stromal cells and osteoblastic cells of the hematopoietic niches are the major sources of M-CSF [21]. The comparison of two transgenic mouse lines, $Csf1r^{-}/Csf1r^{-}$ and $Csf1^{op}/Csf1^{op}$, confirmed the fundamental role of M-CSF in the production and differentiation of monocytes. Both mouse lines showed a reduced number of circulating monocytes and a decreased number of tissue resident macrophages [22]. In case of MI, different animal models showed an increased expression of M-CSF in cardiac tissue [23]. Another study showed that the administration of recombinant M-CSF in mice with MI induces the egress of monocytes from the BM via modulating the CXC-chemokine receptor 4 (CXCR4)-XC-chemokine ligand 12 (CXCL12) axis [24].

3. Development of Alternative Phenotypes of Myeloid Cells (Qualitative Alterations)

Several studies showed that pathological conditions such as infections, tumors or tissue injuries stimulate the production of myeloid cell with alternative phenotypes [25][26][27]. For instance, in a mouse model of cancer, distinct subpopulations of neutrophils have been identified. These different subpopulations can be distinguished according to their densities: “normal” and “low-density” neutrophils (LDNs). LDNs showed features associated with pro-tumor activity [28]. Another study identified a subtype of neutrophil with DC-like phenotype which express MHCII and CD11c. DC-like neutrophils differentiate from canonical neutrophils (with a rate <2%) in humans and mice under local and systemic inflammation [29]. Similar to neutrophils, monocytes with alternative phenotypes were identified. For instance, monocytes may develop a “neutrophil-like” phenotype (NeuMo) in response to LPS injection or monocytes may express Ceacam1 and Msr1 (SatM) in case of pulmonary fibrosis [30][31]. Further, a subtype of $Ly6C^{HI}$ monocytes, expressing Sca-1 and MHCII, was found to be induced by interferon gamma (INFγ) [32]. Finally, $Ym1^{+}Ly6C^{HI}$ monocytes are released from the BM during the resolution phase of colitis [33].

There are no evidences regarding particular subsets of circulating monocytes or neutrophils triggered by MI, but future studies may fill this gap [6][27]. The general view is that myeloid cells acquire effector functions as a result of interactions with local signals/the local environment in the ischemic area of the heart. However, a recent study showed that the type I interferon (IFN) response to ischemic cardiac injury begins “remotely” already in the BM. Specifically, the authors showed that myeloid cells are characterized by the expression of IFN-stimulated genes after the MI, already at the level of the BM. This response occurs not only in monocytes or monocyte-derived macrophages, but also in neutrophils [34]. Another work identified the expansion of particular subsets of monocytes ($CD14^{+}$ $HLA\text{-}DR^{-}$) and immature neutrophils ($CD16^{+}$ $CD66b^{+}CD10^{-}$) in the blood of patients with MI [35]. These two studies provide a clear confirmation that MI induces quantitative and qualitative changes in the myeloid repertoire.

4. Extramedullary Emergency Source of Myeloid Cells

Although the BM is the primary tissue responsible for the production of leukocytes, extramedullary hematopoiesis takes place in the spleen after the onset of the MI. As shown by Swirski and colleagues, the spleen is a reservoir of $Ly6C^{HI}$ and $Ly6C^{LOW}$ monocytes and, in case of splenectomy, leukocyte supply to the infarcted heart is reduced [36]. Within the first days after MI, a huge quantity of monocytes is released from the splenic subcapsular red pulp

into the circulation. The mobilization of monocytes is driven by the interaction of angiotensin II with its receptors expressed by monocytes [37]. Consistently, the recent development of a high-density lipoprotein-derived nanotracer, which allows non-invasive in vivo tracking of myeloid cells, demonstrates that in case of permanent or transient LAD ligation, a significant quantity of myeloid cells is mobilized from the spleen [38]. As a consequence, the number of splenic Ly6C^{HI} monocytes decrease starting from day 1 post-MI and is restored within 4 days [39]. Splenic monocytes derive from maturation of HSPCs which egressed the BM and seeded the spleen prior. HSPCs are retained in the spleen by the presence of macrophages expressing vascular cell adhesion protein-1 (VCAM-1) [40]. Further, Grisanti and colleagues using chimeric mice with β2AR knockout reconstituted BM showed that the deletion of the β2-adrenoreceptor (β2AR) induces retention of leukocytes in the spleen due to an overexpression of VCAM-1. Moreover, the expression of both VCAM-1 and CCR2 appears to be regulated by β2AR signaling [41][42]. Further, these and others studies demonstrated the efficacy of β-blockers as treatment for MI [42][43][44]. Finally, the administration of bromodeoxyuridine (BrdU) showed a robust expansion of myeloid progenitor cells (MDPs) in the spleen after LAD ligation. Similar to the BM, IL-1β regulates the production of splenic monocytes after MI [45].

Splenic neutrophils take part in the response to bacteria, like in the case of *Streptococcus pneumoniae* infection, and it has been demonstrated that pancreatic carcinoma or sepsis causes extramedullary granulopoiesis [46][47]. Unlike monocytes, it is not entirely clear whether the spleen also functions a source of neutrophils in case of MI, so further studies are needed to clarify this aspect.

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